REMARKS

The Examiner rejected claims 1, 3-7, and 24-27. Claim 27 has been canceled herein without prejudice. Thus, claims 1, 3-7, and 24-26 are pending, and claims 8 and 12-23 stand withdrawn.

Claim 1 has been amended herein to recite that the purified polypeptide can be a variant of a wild-type ICOS amino acid sequence consisting of a fragment of at least 15 amino acids of the extracellular domain, that the variant consists of an amino acid sequence that differs by one or more amino acid substitutions from, but is at least 85% homologous to, its corresponding wild-type ICOS amino acid sequence, and that the polypeptide consists of an amino acid sequence that has altered affinity for human B7-H2 compared to its corresponding wild-type ICOS amino acid sequence, wherein the affinity for human B7-H2 is increased by at least 10% relative to the affinity of the corresponding wild-type ICOS amino acid sequence for human B7-H2 (emphasis added). Withdrawn claim 12 has been amended for consistency with claim 1. Support for these amendments can be found in Applicants' specification at, for example, page 5, line 13 to page 6, line 5, page 7, lines 3-7, page 18, lines 15-23, and page 24, line 5 to page 25, line 20. These sections of the specification disclose, *inter alia*, that an ICOS polypeptide can be at least 5 amino acids in length, can be at least 75% homologous to the corresponding portion of the wild type ICOS polypeptide, and can bind to human B7-H2 with an affinity that is increased by at least 10%. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1, 3-7, and 24-26.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 1, 3-7, and 24-27 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner stated that the claims are indefinite in the recitation of "B7-H2" because its identity is unclear. Stating that Applicants' previous arguments citing the specification were unpersuasive, the Examiner asserted that the specification does not sufficiently define the metes and bounds of the invention (i.e., whether polypeptides of species other than mouse and human are encompassed within the scope of the claims, and whether other B7-related proteins also are encompassed).

Applicants respectfully disagree. The metes and bounds of the claims with regard to "B7-H2" are clear from the specification. To further prosecution, however, Applicants have amended claim 1 to recite that the variant has altered affinity for human B7-H2. Thus, the present claims are definite.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 3-7, and 24-26 under 35 U.S.C. § 112, second paragraph.

The Examiner rejected claims 3-6 under 35 U.S.C. § 112, second paragraph, as being indefinite for depending from canceled claims. Applicants have amended claims 3 and 5 to depend from claim 1. In light of these amendments, this rejection is moot.

The Examiner rejected claims 1, 3-7, and 24-27 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to a person skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. Specifically, the Examiner alleged that the previous amendment to claim 1 constitutes new matter, because the specification "does not appear to provide an adequate written description of a 'variant consisting of an amino acid sequence that **differs by one or more amino acid substitutions** from [ ] its corresponding wild-type ICOS amino acid sequence.'" (Office Action at page 4; emphasis in original.) The Examiner also alleged that the specification does not provide sufficient support for the generic recitation of a fusion polypeptide comprising ICOS and an "**immunoglobulin Fc fragment** sequence" (emphasis in original) as recited in claim 26, which was newly added in the Amendment and Reply filed on October 6, 2005.

Applicants respectfully disagree with these rejections. The previous amendment to claim 1 regarding the phrase "differs by one or more amino acid substitutions" does not constitute new matter, as it is supported by the specification. For example, Applicants' specification at page 6, lines 6-27 discloses that an ICOS polypeptide can contain mutations relative to the wild-type ICOS protein, such that an ICOS polypeptide can include changes in its amino acid sequence as compared to a wild-type ICOS protein. Further, Applicants' specification at page 7, lines 28-31 discloses that ICOS mutations can involve more than one amino acid or a single amino acid.

Thus, Applicants' specification clearly supports the recitation of "differs by one or more amino acid substitutions" in claim 1.

Applicants' specification also provides support for the phrase "immunoglobulin Fc fragment" recited in claim 26 as previously presented. For example, Applicants' specification at page 11, lines 24-31 discloses that an ICOS polypeptide can be linked to an immunoglobulin sequence such that an ICOSIg polypeptide is produced. Further, Applicants' specification at page 18, lines 15-18, discloses that a fusion polypeptide was prepared containing ICOS and IgG1 sequences. Thus, the recitation of "an immunoglobulin Fc fragment" in claim 26 does not constitute new matter.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 3-7, and 24-26 under 35 U.S.C. § 112, first paragraph.

The Examiner maintained the rejection of claims 1-3, 5, and 7, and also rejected claims 24-27, under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner stated that while the specification is enabling for a polypeptide that differs from SEQ ID NO:12 by the specific substitutions recited in claims 4 and 6, it does not reasonably provide enablement for the genus including polypeptides at least 75% homologous to wild-type ICOS and polypeptides comprising fragments of at least 8 amino acids of the extracellular domain of ICOS. The Examiner concluded that given the number of polypeptides encompassed by the claims, and the fact that only a small proportion of those are expected to possess the requisite functional properties, undue experimentation would be required to make and use the claimed polypeptides.

Applicants respectfully disagree. A person of ordinary skill in the art reading Applicants' specification at the time it was filed would have been able to make and use the presently claimed polypeptides. This is particularly true given the level of skill in the art and the teachings of Applicants' specification. For example, Figure 2 of Applicants' specification provides an alignment of the extracellular Ig domains of mouse and human ICOS, together with eight other related proteins. The alignment indicates regions that are conserved. Further, Applicants' specification at, for example, page 5, lines 3-10; page 6, line 28; page 7, line 28 to page 8, line 5; page 23, lines 11-20; page 23, line 30 to page 24, line 2; and page 24, lines 5-23 discloses that the ICOS ligand binding domain is thought to include amino acids 49-52, 64-68, 75-78, and 114-

119 of SEQ ID NO:12, and that mutation of these residues can result in polypeptides with altered binding affinity. Thus, only 19 amino acids out of the 111 amino acid extracellular ICOS sequence set forth in SEQ ID NO:10 are suggested to be involved in ligand binding. A person of ordinary skill in the art would readily have been able to use standard methods to make and purify an ICOS polypeptide containing a substitution at one or more of these positions, particularly since examples of such methods are set forth Applicants' specification. See, e.g., the sections of Applicants' specification at page 7, lines 8-27, page 9, lines 5-29, and page 18, line 30 to page 19, line 14, which disclose methods for making and purifying variant ICOS polypeptides.

A person of ordinary skill also would have been able to determine whether a variant ICOS amino acid sequence is at least 85% homologous to the corresponding wild type ICOS amino acid sequence, as methods for determining percent identity are set forth at page 6, lines 2-5 of Applicants' specification. Further, a person of ordinary skill would have been able to determine whether a variant ICOS polypeptide has reduced binding affinity for human B7-H2 as compared to a wild type ICOS polypeptide, particularly since examples of such methods are described in Applicants' specification at page 21, line 16 to page 22, line 10. Methods for making and testing variant ICOS polypeptides also are set forth in Example 3 of Applicants' specification (see, page 24, line 5 to page 25, line 20). In addition, a person of ordinary skill would have been able to use a variant ICOS polypeptide to inhibit a T cell response, particularly since Applicants' specification at page 22, lines 11-30 and page 26, line 13 to page 27, line 14 sets forth examples of such methods. Thus, the instant specification would have adequately enabled a person of ordinary skill in the art at the time the application was filed to make and use the presently claimed polypeptides.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1-3, 5, 7, and 24-26 under 35 U.S.C. § 112.

Rejection under 35 U.S.C. § 102

The Examiner maintained the rejection of claims 1 and 7, and also rejected claims 24-26, under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent Publication No. 2002/01562424 (the Tamatani *et al.* reference). The Examiner stated that although no specific substitutions are mentioned in the Tamatani *et al.* reference, no specific substitutions are recited in claim 1 either.

The Examiner further stated that the Tamatani *et al.* reference teaches variant ICOS polypeptides that inherently would have altered activity. In addition, the Examiner stated that the Tamatani *et al.* reference teaches fusion polypeptides comprising an ICOS variant and a human Ig heavy chain or portion of the constant region.

Applicant respectfully disagrees. The Tamatani *et al.* reference does not anticipate the previously presented claims. For example, the Tamatani *et al.* reference fails to set forth an ICOS amino acid sequence containing any actual substitutions as compared to a wild-type ICOS amino acid sequence. In addition, the Tamatani *et al.* reference fails to make any mention of B7-H2, let alone requiring a substituted ICOS molecule to have altered affinity for B7-H2. Although the Tamatani *et al.* reference mentions polypeptides having at least 60% homology to ICOS, the courts have stated that such theoretical disclosures should not preclude patentability of actual reductions to practice. The CCPA said in *In re Wiggins et al.*, 179 USPQ 421, 425 (CCPA 1973): "[L]ists of thousands of theoretically possible . . . [inventions] could be generated and published which, assuming it would be within the level of the skill in the art to make them, would bar a patent to the actual discoverer of . . . [the invention] no matter how beneficial to mankind it might be. In view of the fact that the purpose sought to be effectuated by the patent law is the encouragement of innovation, such a result would be repugnant to the statute." Thus, Applicants submit that the Tamatani *et al.* reference does not anticipate claim 1 as previously presented.

To further prosecution, however, claim 1 has been amended herein to recite that the polypeptide consists of an amino acid sequence having affinity for human B7-H2 that is increased by at least 10% relative to the affinity of the corresponding wild-type ICOS amino acid sequence for human B7-H2. At no point does the Tamatani *et al.* reference disclose, either directly or inherently, any ICOS polypeptide containing a substitution that has affinity for B7-H2 that is increased by at least 10% relative to the affinity of the corresponding wild-type ICOS amino acid sequence. Thus, the Tamatani *et al.* reference does not anticipate the present claims.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 7, and 24-26 under 35 U.S.C. § 102(e).

CONCLUSION

Applicants submit that claims 1, 3-7, and 24-26 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please apply the two month extension of time fee of $225, and any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

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